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REVIEW

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Administration of dehydroepiandrosterone improves endometrial thickness in women undergoing IVF/ICSI: a systematic review and meta-analysis

Ling Huang[1], Ying Gao[2], Shuo Liang[3] and Mei Jiang[4*]

Abstract

Background The positive effects of dehydroepiandrosterone (DHEA) on oocyte and embryo quality improvement are often concerned. While the results on DHEA-induced endometrial improvement are controversial.

Objective To evaluate whether DHEA intervention improved endometrial function and reproductive outcomes during in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles and to thus provide clinical recommendations.

Data sources PubMed, Cochrane Library, EMBASE and Web of Science from database inception to 31 July 2024, without language restrictions. The references of conference proceedings and websites on clinical trials were manually checked.

Study design Systematic review and meta-analysis.

Study eligibility criteria Parallel-controlled randomized controlled trials (RCTs) design; women underwent IVF/ICSI, patients in the experimental group received adminstration with DHEA, whereas the control group received with or without placebo; and the outcomes included reproductive or endometrial function.

Study appraisal and synthesis methods RCTs evaluating the effects of DHEA on IVF/ICSI outcomes were included. Risk of bias and quality of evidence (QoE) were assessed according to the Cochrane Collaboration's tool and the Grading of Recommendations Assessment, Development and Evaluation system. Odds ratios (ORs) and mean differences (MDs) with 95% confidence intervals (CIs) were assessed by random-effects or fixed-effects models. Subgroup and meta-regression analyses were used to find sources of heterogeneity. Trial sequential analysis was used to judge the stability of the outcomes. Trial sequential analysis was used in order to control for random errors.

Results A total of 16 trials included 1973 women. DHEA treatment significantly increased endometrial thickness (MD = 0.93, CI: 0.27 to 1.60; low QoE), which helped improve clinical pregnancy rate (CPR) (OR = 1.34, 95% CI: 1.08 to 1.67; low QoE). DHEA administration also increased the quality of oocyte and embryo [including the number of oocytes retrieved (MD = 0.73, CI: 0.36 to 1.10; low QoE), oocytes fertilized (MD = 0.48, CI: 0.10 to 0.87; low QoE), transferred embryos (MD = 0.27, CI: 0.09 to 0.46; very low QoE), and high-quality embryos (MD = 0.65, CI: 0.27 to 1.03; low QoE)]. Subgroup and meta-regression analyses revealed that heterogeneity might be related to disease type,

*Correspondence:
Mei Jiang
jiangmei@bucm.edu.cn
Full list of author information is available at the end of the article

ovarian stimulation protocol, and addition time of DHEA treatment. There was insufficient evidence to reach a conclusion regarding the live birth rate/ongoing pregnancy rate, miscarriage rate, and MII oocyte number of DHEA. And no severe adverse effects were observed with DHEA administration. Due to the apparent improvemen in the CPR, women with thin endometrium might benefit from DHEA cotreament.

Conclusions Due to the limited sample size and methodological problems, the QoE was low to very low; hence, the results should be interpreted with caution. The effectiveness of DHEA requires more research before it can be considered for clinical practice.

PROSPERO registration CRD42023428885.

Keywords Dehydroepiandrosterone, Endometrial thickness, Live birth, Clinical pregnancy, *In vitro* fertilization/Intracytoplasmic sperm injection

Introduction

The successful implantation of embryos requires healthy embryos, endometrial receptivity, and constant interaction at the mother–fetus interface. Endometrial receptivity refers to a state of the endometrium in which the endometrium allows the embryo to adhere to, penetrate, and cause changes in the endometrium stroma leading to implantation [43], and it determines the success of embryo implantation [32]. The hyperphysiological hormone environment resulting from ovarian stimulation is not conducive to the establishment of endometrial receptivity during assisted reproductive technology (ART) [22]. Hence, identifying methods to improve endometrial receptivity and synchronize embryo development with endometrium is the key to improve the success of ART. Evidence–based treatment programs are needed to effectively and safely solve the problems related to endometrial function.

Recently, the role of dehydroepiandrosterone (DHEA) in female reproduction has garnered increasing attention. DHEA can slow and reverse the effects of aging and increase fertility in women with diminished ovarian reserve (DOR) and poor ovarian response (POR) [45]. DOR was defined as those who presented regular cycles, antral follicle count (AFC) < 5, and anti-Mullerian hormone (AMH) < 1.1 ng/mL, in line with the POSEIDON criteria [5]. According to the'Bologna'criteria [7], POR women should fulfill at least two out of the following criteria: (1) advanced maternal age (≥ 40 years) or the presentation of other risk factors for an insufficient response, such as previous ovarian surgery, genetic defects, chemotherapy or autoimmune disorder; (2) a former episode of poor ovarian response (≤ 3 oocytes with a conventional stimulation protocol); and (3) a low ovarian reserve with an AFC less than 5 ~ 7 follicles and serum AMH less than 0.5 ~ 1.1 ng/mL. Patients with high follicle-stimulating hormone (FSH) or low AMH levels had an increased likelihood of becoming pregnant after DHEA administration [11, 23]. Hence, DHEA is widely used in clinical practice during ART, especially for improving pregnancy rates and oocyte quality [10, 29, 40]. Recent research has shown that DHEA might provide an additional potential benefit for endometrial receptivity [27, 39]; however, some studies have reported inconsistent results [9, 30].

Several systematic reviews and meta-analyses have examined the role of DHEA therapy during in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) [19, 21, 28, 29, 31, 37, 51]. Nagels et al. [28] analyzed 8 randomized controlled trials (RCTs) comprising a total of 878 participants and reported that DHEA increased live birth rate (LBR) or ongoing pregnancy rate; nonetheless, its effects on oocyte count, MII oocyte count, and the number of transplanted embryos are unclear. Consistent with Nagels et al. 's findings, Schwarzeet al. [19, 21, 37] have shown that DHEA administration improves the ovarian reserve, leading to high LBR. However, conclusions from meta-analyses were not comprehensive, as they mainly focused on individuals with DOR, pregnancy outcomes, oocytes, and embryo quality, while effects in other populations and on endometrial function had been largely ignored. Despite the widespread use of DHEA in ART, there is little consensus on the timing of administration and and the IVF protocols selected hindering the application of DHEA during ART. Therefore, a systematic review and meta-analysis of collected randomized controlled trial data is warranted to comprehensively understand the effects of DHEA administration on different populations and endometrium during IVF cycles.

Methods

Protocol and registration

This systematic review had been prospectively registered in Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42023428885, and was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [26].

Search strategy

To identify eligible studies, an exhaustive literature search was conducted in PubMed, the Cochrane Library, EMBASE and Web of Science databases, which were without restricting by language, from their inception to 31 July 2024. Furthermore, to obtain additional potentially relevant research, the references of conference proceedings and websites on clinical trials were manually checked. The details of the search in above databases were shown in Supplementary Table S1-S4.

Inclusion and exclusion criteria

The inclusion criteria for eligible studies were as follows: (i) parallel-controlled RCT design; (ii) women underwent IVF/ICSI, the experimental group received DHEA administration, while the control group received with or without placebo; and (iii) the outcomes included reproductive or endometrial function. The reproductive outcomes consisted of LBR, (when live birth rate was not reported, ongoing pregnancy rate was chosen as a surrogate), clinical pregnancy rate (CPR), and miscarriage rate (MR). Endometrial outcomes included endometrial thickness (EMT) and endometrial morphology. The primary outcomes included LBR/ongoing pregnancy rate (or CPR if LBR/ongoing pregnancy rate was not reported) and EMT. The secondary outcomes were MR, endometrial morphology, oocyte and embryo quality.

The exclusion criteria were as follows: studies include laboratory or animal studies, reviews, cohort or case-control studies, case reports or quasi-randomized trials.

Study selection and data extraction

Literature screening and data extraction were carried out independently by two researchers (MJ and YG). Discrepancies between the two reviewers were resolved in consultation with the third researcher (LH). First, import citations into EndNote to identify duplicate citations. Second, research titles and abstracts were screened to exclude content that did not meet the inclusion criteria. Finally, read the full literature and further exclude studies according to the inclusion and exclusion criteria. When no continuous variables were reported, each author was contacted via email and asked for raw data. Extract the following information from the included studies: study characteristics including first author, year of publication and location; participant characteristics including population, sample size and age; IVF procedures; DHEA protocol consisted of dose, frequency and duration; data on the targeted outcomes; and adverse events.

Risk of bias and quality assessment

The methodological quality of eligible trials was assessed by three researchers (MJ, YG, and SL) according to the Cochrane Collaboration's tool. Low, unclear, or high risk of research bias was determined by selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Referring to the method of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [12], quality of evidence (QoE) was graded according to the study design, study quality, inconsistency, indirectness and imprecision.

Statistical analysis

For dichotomous data, the results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous data, the results were pooled for meta-analysis as the mean difference (MD) with 95% CIs. The Cochran's Q two-sided homogeneity test [13] was used to test for heterogeneity of the studies. A Mantel-Haenszel fixed-effect model was used if I-square (I^2) < 50%, and if not, a DerSimonian-Laird random-effects model was used [15].

Subgroup analyses and meta-regression analyses were performed to determine the effects of DHEA administration and study characteristics, and to test whether this could explain heterogeneity. Moreover, sensitivity analyses were performed to examine the robustness of pooled estimates. When the inclusion number was > 9, the funnel plot method, was used to investigate the potential publication bias of the primary outcomes. RevMan 5.4 software was used for the meta analysis, and R 4.4.2 software was used for the meta-regression analyses and sensitivity analyses. Statistical significance is dependent on whether P value is less than 0.05.

Trial sequential analysis (TSA) was able to reduce risks of random error arising from inadequate sample size or repetitive tests and help estimate the required information size (RIS) for meta-analysis. TSA was performed for primary outcomes using TSA V.0.9.5.10 Beta software. Type 1 error and power were set as 5% and 80%, respectively.

Results

Study selection and characteristics

A total of 562 articles were identified in the preliminary search. After eliminating duplicates, 363 records were evaluated by screening the titles and abstracts. After screening, 59 studies were selected for full-text review, 43 of which were excluded because they did not meet the inclusion criteria. In the end, 16 studies matched this meta-analysis. The details of the screening and

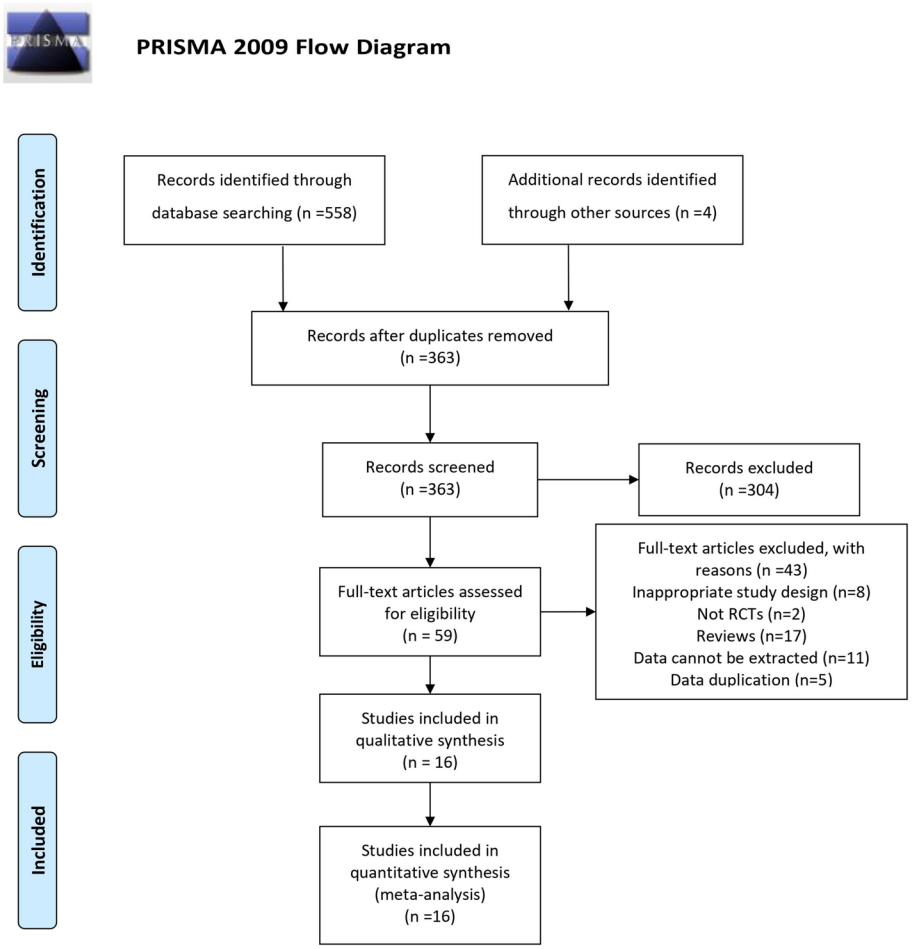

Fig. 1 Flow chart of the selection process

selection process were outlined in the PRISMA flow diagram (Fig. 1).

All studies were parallel-design and RCTs conducted in Israel [44], Italy [1, 39], United Arab [25], Turkey [16], China [9, 18, 42, 47–50, 52], Egypt [17], UK [30], Iran [27] between 2010 and 2022. A total of 1973 women undergoing IVF/ICSI were included in this analysis, with seven trials performed with women with POR, four trials with women with DOR, one trial with women with endometriosis and four trials with normal responders. The IVF procedure varied among trials. Gonadotropin-releasing hormone agonist (GnRH-a) long/short and gonadotropin-releasing hormone antagonist (GnRH-A) were the major interventions; and the rest were administered by microflare stimulation. Regarding DHEA administration, the dosage was all 75 mg/d, and the course of treatment ranged from 4 to 18 weeks. Table 1 showed the characteristics of the included studies.

Risk of bias of included studies

Fourteen studies were deemed to have a low risk of selection bias due to adequate randomization methods (the use of computer-generated list or random number table). Six studies with the use of sealed opaque envelopes were judged as low risk of allocation concealment; two studies without allocation concealment had a high risk; the rest had an unclear risk due to lack of information given. Seven studies with double-blind had a low risk of performance bias; one study had an unclear risk due to lack of details provided; the rest were deemed to have a high risk. Five studies with three-blind were considered as low risk of detection bias; six studies had an unclear risk due to lack of information given; the rest lacked detection blind had a high risk. Two studies with high drop outs were judged as having a high risk of attrition bias; and only one study had an unclear risk due to lack of details provided; the rest were considered as low risk. Six studies without clinical trial registration or LBR/ongoing pregnancy

Table 1 Summary characteristics of studies and participants

Study	Country	Population	Sample size (*n*)		Age (y)		IVF procedure	DHEA protocol	Placebo	Outcomes	Adverse events
			DHEA	CON	DHEA	CON					
Wiser (2010) [44]	Israel	POR	17	16	36.90 ± 4.70	37.80 ± 4.60	GnRH-a long	75 mg orally, once a day, at least 6 weeks before starting the first cycle of ovulation induction. Patients who did not conceive and continued to the second cycle took DHEA for at least 16–18 weeks.	No	• LBR and CPR • EMT • Number of oocytes retrieved and transferred embryos, fertilization rate and mean score of leading embryo transfer	None that were DHEA related
Artini (2012) [1]	Italy	POR	12	12	36.58 ± 3.32	37.00 ± 4.61	GnRH-A	25 mg three times daily, orally, for 3 months before IVF cycle	No	• CPR • Number of oocytes retrieved, MII oocytes and transferred embryos • fertilized oocytes and high-quality embryos (I-II)	Increased sebum production and transitional hirsutism, but no patient dropped out.
Moawad (2012) [25]	United Arab	POR	67	66	37.40 ± 6.40	37.10 ± 7.20	GnRH-a short	25 mg orally, three times a day, for at least 12 weeks before starting ovulation induction.	No	• CPR and ongoing pregnancy rate • EMT • Number of oocytes retrieved, MII oocytes, fertilization rate and transferred embryos	Developed transitional acne, an improved feeling of well-being and increased libido, but no patient dropped out.
Kara (2014) [16]	Turkey	DOR	104	104	30.97 ± 5.76	31.15 ± 5.58	Microflare stimulation	25 mg t.i.d. for 12 weeks.	No	• CPR • Number of oocytes retrieved, MII oocytes and fertilization rate	NA

Table 1 (continued)

Study	Country	Population	Sample size (*n*)		Age (y)		IVF procedure	DHEA protocol	Placebo	Outcomes	Adverse events
			DHEA	CON	DHEA	CON					
Yeung (2014) [48]	China	POR	16	16	36 (35–38)	37 (35–38)	GnRH-A	25 mg, three times a day (i.e., 75 mg per day) for 12 weeks.	Yes	• LBR, CPR, MR and ongoing pregnancy rate • EMT • Number of oocytes retrieved, fertilized embryos, transferred embryos and top-quality embryos.	No major adverse effects were reported during the study period other than increased acne.
Zhang (2014) [50]	China	DOR	42	53	37.17 ± 5.22	37.43 ± 4.33	Microflare stimulation	25 mg three times per day for three consecutive menstrual cycles prior to IVF cycles.	No	• CPR • Number of oocytes retrieved, MII oocytes, transferred embryos and the accumulated score of embryos.	No major adverse effects were reported, except for dizziness and acne.
Tartagni (2015) [39, 40]	Italy	Normal responders aging 36–40 years	53	56	37.10 ± 2.20	37.40 ± 2.90	GnRH-a long	75 mg/d, orally, 8 weeks before starting the cycle of ovulation induction	Yes	• LBR, CPR and MR • EMT • Number of oocytes retrieved, MII oocytes, transferred embryos and high quality embryos replaced.	None that were DHEA related.
Yeung (2015) [47]	China	Normal responders	36	36	35 (33–37)	33 (32–38)	GnRH-A	25 mg, three times a day for 12 weeks.	Yes	• LBR, CPR, MR, ongoing pregnancy rate and multiple pregnancy rate • Number of oocytes retrieved, fertilized embryos, transferred embryos and high-quality embryos.	No major adverse effects were reported, except for hot flushes and insomnia in DHEA group; headache and dyspepsia in placebo group.

Table 1 (continued)

Study	Country	Population	Sample size (*n*)		Age (y)		IVF procedure	DHEA protocol	Placebo	Outcomes	Adverse events
			DHEA	CON	DHEA	CON					
Kotb (2016) [17]	Egypt	POR	70	70	40.05 ± 3.10	39.7 ± 0.50	GnRH-A	Oral, 25 mg three times daily for three months before IVF/ICSI	No	• CPR and ongoing pregnancy rate • Number of oocytes retrieved, MII oocytes, fertilized oocytes, transferred embryos and excellent embryos.	Mild oily skin.
Yuan (2016) [49]	China	DOR	98	95	31.85 ± 2.64	31.26 ± 3.15	GnRH-a long	Oral, 25 mg three times daily for three months before IVF	Yes	• CPR • Number of oocytes retrieved, fertilization rate and high-quality embryo formation rate.	NA
Fu (2017) [9]	China	DOR	58	58	37.40 ± 3.60	36.80 ± 4.30	Microflare stimulation	25 mg three times a day for 12 weeks prior to IVF/ICSI treatment	No	• CPR • EMT • Number of oocytes retrieved, MII oocytes, transferred embryos, fertilized embryos and high-quality embryos replaced.	No major adverse effects were reported, except for poor appetite and acne.
Narkwichean (2017) [30]	United Kingdom	POR	27	25	36.80 ± 3.90	35.20 ± 5.30	GnRH-a long	75 mg, orally once daily for at least 12 weeks before and during controlled collection.	Yes	• LBR, CPR and MR • EMT • Number of oocytes retrieved and fertilisation rate.	Non-specific gastrointestinal (GI) disturbance (nausea), acne and oily skin
Mostajeran (2018) [27]	Iran	Normal responders aging > 35 years	45	49	37.07 ± 1.19	37.24 ± 1.27	GnRH-a long	25 mg three times daily, orally 8 weeks before IVF	Yes	• CPR and MR • EMT	NA

Table 1 (continued)

Study	Country	Population	Sample size (*n*)		Age (y)		IVF procedure	DHEA protocol	Placebo	Outcomes	Adverse events
			DHEA	CON	DHEA	CON					
Li (2021) [18]	China	Normal responders aging > 38 years	20	25	40.80 ± 2.70	41.30 ± 3.40	NA	25 mg three times daily for at least 8 weeks before IVF	No	• LBR, CPR and ongoing pregnancy rate • Number of oocytes retrieved, MII oocytes, top-quality D3 embryos and fertilized rate.	NA
Zhang (2021) [52]	China	Endometriosis	22	22	37.46 ± 2.17	38.61 ± 2.93	GnRH-a long	25 mg orally 3 times a day for 90 days before IVF	Yes	• LBR, CPR and ongoing pregnancy rate • Number of oocytes retrieved, transferred embryos, excellent embryos, fertilized oocytes, and fertilized rate.	NA
Wang (2022) [42]	China	POR	301	305	39.00 ± 4.64	39.53 ± 4.39	GnRH-a short	25 mg three times daily for 4–12 weeks before oocyte retrieval	Yes	• LBR, CPR, MR and continuing pregnancy rate • Number of oocytes retrieved, fertilized oocytes, and high-score embryos.	NA

DHEA dehydroepiandrosterone, *GnRH-A* gonadotrophin-releasing hormone antagonist, *GnRH-a* gonadotrophinreleasing hormone agonist, *LBR* live birth rate, *CPR* clinical pregnancy rate, *MR* miscarriage rate, *EMT* endometrial thickness, *NA* not available, *POR* poor ovarian response, *DOR* diminished ovarian reserve

rate were deemed to high risk of reporting bias. Others sources of bias were judged as having a unclear risk in all trials, except one trial had a free DHEA supply (Supplementary Fig. S1).

Synthesis of results

Live birth rate/ongoing pregnancy rate

The effects of DHEA on LBR/ongoing pregnancy rate were reported in ten trials [17, 18, 25, 30, 39, 42, 44, 47, 48, 52] with a total of 1217 participants. The pooled effects suggested that DHEA administration had no advantages in raising the rate of live birth or ongoing pregnancy (OR = 1.33, 95% CI: 0.98 to 1.82; $P = 0.07$; $I^2 = 38\%$) (Fig. 2A). The QoE was low due to serious risk of bias and wide CI (Table 2). In terms of subgroup analyses, significant effects of DHEA on LBR/ongoing pregnancy rate were found in women over 40 years compare to women under 40 years. In addition, patients cotreated with GnRH-a long protocols achieved a higher LBR/ongoing pregnancy rate than the other ovarian stimulation protocols (such as GnRH-a short and GnRH-A protocols). Regarding time of DHEA treatment, patients treated with DHEA for 8 weeks achieved a higher LBR/ongoing pregnancy rate than the other administration time (Table 3).

Clinical pregnancy rate

CPR was reported in 15 trials (1949 total participants) [9, 16–18, 25, 27, 30, 39, 42, 44, 47, 48]. Overall, the CPR in the DHEA group was significantly higher than that in the control group (OR = 1.34, 95% CI: 1.08 to 1.67; $P = 0.009$; $I^2 = 20\%$) (Fig. 2B), however, the QoE was low (Table 2). In subgroup analyses, significant effects of DHEA on CPR were observed in women with DOR compared to other disease types. Regarding mean age, DHEA administration on women over 40 years had a greater benefit than women under 40 years. In addition, women treated with DHEA for 8 weeks and 12weeks achieved higher CPR than the other subgroups (Table 4).

Endometrial thickness

Seven trials with 559 total participants evaluated the effects of DHEA on EMT [9, 25, 27, 30, 39, 44, 48]. Significant increases in EMT were found in the DHEA group (MD = 0.93, CI: 0.27 to 1.60; $P = 0.006$; $I^2 = 81\%$) (Fig. 2C). The QoE was low due to serious risk of bias and inconsistency (Table 2). Subgroup analyses showed more obvious improvement in EMT on normal responders than the others (such as women with POR or DOR). In addition, administering DHEA for 8 weeks or during GnRH-a short protocols had a greater effect than the other administration times or protocols (Table 5).

Miscarriage rate

Six studies reported the MR [27, 30, 39, 42, 47, 48]. The pooled effects suggested that no advantages of DHEA administration in reducing the rate of miscarriage (OR = 0.83, 95% CI: 0.45 to 1.53; $P = 0.56$; $I^2 = 28\%$) (Supplementary Fig. S2A). The QoE was low (Table 2), and no differences were found in subgroup analyses (Supplementary Table S5).

Number of oocytes retrieved

Fifteen trials with a total of 1829 participants investigated the effect of DHEA on the number of oocytes retrieved [1, 9, 16–18, 25, 30, 39, 42, 44, 47–50, 52]. The pooled data of the studies showed that DHEA group had more retrieved oocytes than control group (MD = 0.73, CI: 0.36 to 1.10; $P = 0.0001$; $I^2 = 70\%$) (Supplementary Fig. S2B). The QoE was low (Table 2). Subgroup analyses revealed that women with DOR had more retrieved oocytes than the others. And benefits were found in women both over 40 years and under 40 years. In addition, DHEA treatment resulted in more retrieved oocytes during microflare stimulation, GnRH-A and GnRH-a long protocols, but no advantages were noted in GnRH-a short protocols. In terms of DHEA administration times, DHEA treatment for 12 weeks or 8 weeks led to more retrieved oocytes (Supplementary Table S6).

Number of MII oocytes

Eight studies, including 842 total patients, provided information on the number of MII oocytes [1, 9, 16–18, 25, 39, 50]. The results suggested that DHEA did not increase the number of MII oocytes (MD = 0.56, CI: −0.06 to 1.18; $P = 0.07$; $I^2 = 97\%$) (Supplementary Fig. S2C), with evidence of very low quality (Table 2). Subgroup analyses concerning the disease types indicated that women with DOR had more MII oocytes than the others. Moreover, administering DHEA during microflare stimulation protocols, starting on cycle day 3 of the menses, you will take 2 ~ 3 weeks of oral contraceptive pills then start micro-dose Lupron 3 days after stopping oral contraceptive pills, then add gonadotropins 2 days after starting Lupron, had a greater effect than the other protocols. In addition, improvements were significantly greater among women with advanced age (Supplementary Table S7).

Number of oocytes fertilized

Eight studies with 1077 total patients were included in this analysis [1, 9, 17, 18, 42, 47, 48, 52]. The number of oocytes fertilized in the DHEA group was significantly higher than that in the control group (MD = 0.48, CI: 0.10 to 0.87; $P = 0.01$; $I^2 = 53\%$) (Supplementary Fig. S2D). The

Table 2 DHEA compared to control for [IVF]

Patient or population: patients with [IVF]					
Settings:					
Intervention: DHEA					
Comparison: Control					
Outcomes	**Illustrative comparative risks[a] (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	Control	**DHEA**			
Live birth/ongoing pregnancy rate	**Study population**		**OR 1.33** (0.98 to 1.82)	1217 (10 studies)	⊕⊕⊖⊖ **low** [1,2]
	141 per 1000	**179 per 1000** (139 to 230)			
	Moderate				
	127 per 1000	**162 per 1000** (125 to 209)			
CPR	**Study population**		**OR 1.34** (1.08 to 1.67)	1949 (15 studies)	⊕⊕⊖⊖ **low** [1,2]
	196 per 1000	**246 per 1000** (208 to 289)			
	Moderate				
	160 per 1000	**203 per 1000** (171 to 241)			
MR	**Study population**		**OR 0.83** (0.45 to 1.53)	391 (6 studies)	⊕⊕⊖⊖ **low** [1,2]
	139 per 1000	**118 per 1000** (68 to 198)			
	Moderate				
	123 per 1000	**104 per 1000** (59 to 177)			
EMT		The mean emt in the intervention groups was **0.93 higher** (0.27 to 1.6 higher)		559 (7 studies)	⊕⊕⊖⊖ **low** [1,3]
Number of retrieved oocytes		The mean number of retrieved oocytes in the intervention groups was **0.73 higher** (0.36 to 1.1 higher)		1829 (15 studies)	⊕⊕⊖⊖ **low** [1,3]
Number of MII oocytes		The mean number of mii oocytes in the intervention groups was **0.56 higher** (0.06 lower to 1.18 higher)		842 (8 studies)	⊕⊖⊖⊖ **very low** [1,3,4]
Number of oocytes fertilized		The mean number of oocytes fertilized in the intervention groups was **0.48 higher** (0.1 to 0.87 higher)		1077 (8 studies)	⊕⊕⊖⊖ **low** [1,3]
Number of transferred embryos		The mean number of transferred embryos in the intervention groups was **0.27 higher** (0.09 to 0.46 higher)		1020 (11 studies)	⊕⊖⊖⊖ **very low** [1,2,3]

Table 2 (continued)

Patient or population: patients with [IVF]					
Settings:					
Intervention: DHEA					
Comparison: Control					
Outcomes	**Illustrative comparative risks[a] (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk **Control**	**Corresponding risk** **DHEA**			
Number of good quality embryos		The mean number of good quality embryos in the intervention groups was **0.65 higher** (0.27 to 1.03 higher)		1063 (8 studies)	⊕⊕⊖⊖ **low** [1,3]

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

[a] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

CI Confidence interval, *OR* Odds ratio

[1] Methods of allocation concealment not clearly described, or too many participants lost to follow-up, or high risk of selective reporting bias

[2] Small sample sizes, or very wide CIs

[3] High heterogeneity

[4] Obviously asymmetrical funnel plot

QoE was low (Table 2). Subgroup analyses suggested that women with endometriosis had higher oocytes fertilized than the others. Moreover, administration DHEA with GnRH-A or GnRH-a long protocols increased the number of oocytes fertilized compared to other protocols. In addition, the increase in the number of oocytes fertilized was more pronounced in DHEA administration for 12 weeks (Supplementary Table S8).

Number of transferred embryos

Eleven trials, including 1020 total patients, assessed outcomes concerning the number of transferred embryos [1, 9, 16, 17, 25, 39, 44, 47, 48, 50, 52]. The results showed a significant positive effect of DHEA (MD = 0.27, CI: 0.09 to 0.46; $P = 0.003$; $I^2 = 80\%$), indicating that DHEA treatment led to more transferred embryos (Supplementary Fig. S2E). The QoE was very low due to wide CI, serious risk of bias and inconsistency (Table 2). Subgroup analyses suggested that DHEA treatment with GnRH-a long or short protocols increased the number of transferred embryos than other protocols. Moreover, DHEA administration for 12 weeks led to more transferred embryos. In addition, improvements were more obvious in young women (Supplementary Table S9).

Number of high-quality embryos

Eight trials with 1063 total patients provided information on the number of high-quality embryos, which were defined as those containing 6 ~ 8 even blastomeres with < 10% fragmentation at day 3 [1, 9, 17, 18, 42, 47, 48, 52]. The overall findings favored DHEA administration (MD = 0.65, CI: 0.27 to 1.03;$P = 0.0008$; $I^2 = 79\%$) (Supplementary Fig. S2F), with evidence of low quality (Table 2). Subgroup analyses suggested that women with DOR or endometriosis had more high-quality embryos than the others. And DHEA treatment with GnRH-a long, GnRH-A or microflare stimulation protocols increased the number of high-quality embryos. Moreover, DHEA administration for 12 weeks increased the number of high-quality embryos. In addition, benefits were all noted in young and advanced-age patients (Supplementary Table S10).

Adverse events

Adverse events were reported in 10 trials. No serious adverse effects of DHEA were observed in the DHEA group, except for increased sebum production, slight acne or hirsutism.

Table 3 Effect estimate and heterogeneity of subgroup analysis for LBR/ongoing pregnancy rate

Subgroup	Trials (*n*)	Sample size (*n*)	Effect Estimate OR/MD (95% CI)	I^2	*P*
Average age					
≤ 40	8	1032	1.17 (0.83, 1.65)	37%	0.38
> 40	2	185	2.49 (1.16, 5.36)	0%	0.02
Disease type					
POR	6	923	1.18 (0.81, 1.72)	47%	0.39
Normal	3	226	1.56 (0.86, 2.84)	29%	0.14
Endometriosis	1	68	3.67 (0.68, 19.66)	--	0.13
Ovarian stimulation protocol					
GnRH-a long protocol	4	280	2.10 (1.17, 3.77)	34%	0.01
GnRH-a short protocol	2	648	0.84 (0.51, 1.38)	0%	0.50
GnRH-A protocol	3	244	1.56 (0.84, 2.92)	44%	0.16
NA	1	45	1.83 (0.36, 9.35)	--	0.47
Addition time of DHEA treatment					
12w	6	469	1.46 (0.92, 2.32)	16%	0.11
8w	2	154	2.23 (1.07, 4.66)	0%	0.03
4-12w	1	543	0.73 (0.42, 1.29)	--	0.28
6-18w	1	51	7.20 (0.80, 64.89)	--	0.08

CI confidence interval, *DHEA* dehydroepiandrosterone, *GnRH-A* gonadotrophin-releasing hormone antagonist, *GnRH-a* gonadotrophinreleasing hormone agonist, *LBR* live birth rate, *MD*mean difference, *NA* not available, *OR* odds ratio, *POR* poor ovarian response

Meta-regression analysis

Meta-regression analysis of EMT outcome had been performed for the importance and high heterogeneity of this outcome indicator. The results indicated that there were no significant differences between DHEA and control groups in EMT after adjusting for disease type ($P=0.847$), ovarian stimulation protocol ($P=0.618$), and addition time of DHEA treatment ($P=0.079$). The details were shown in Supplementary Table S11.

Sensitivity analysis and publication bias

The conclusions were stable, and the estimates after sensitivity analysis remained unchanged, except for the results about LBR/ongoing pregnancy rate, CPR, EMT, and the number of MII oocytes, which should be interpreted with caution.

Given that the assessment can be under powered with small numbers of studies (< 10), only primary outcomes with LBR/ongoing pregnancy rate and CPR were considered. As shown in Fig. 3A and B, no asymmetry was found in the funnel plots, indicating the validity and reliability of the conclusions.

Trial sequential analysis

The TSA of live birth rate/ongoing pregnancy rate showed that the cumulative Z- curve did not cross the traditional boundary and trial sequential monitoring boundary. The RIS was estimated to be 11,213 by performing TSA and the cumulative Z-curve did not reach the RIS, suggesting no significant difference in DHEA and the control groups, and additional trials were needed to rule out type I error. The detail is shown in Supplementary Fig. S3.

Discussion

Main findings

In this systematic review and meta-analysis, the effectiveness of DHEA treatment on endometrial function in women with IVF/ICSI was evaluated. These findings replicated and extended those of previous reviews on the role of DHEA in ART. Assisted DHEA not only increased the CPR and number of oocytes retrieved, oocytes fertilized, transferred embryos, and high-quality embryos, but also improved EMT. Therefore, DHEA may promote fertility by improving ovarian and endometrial quality. Additionally, subgroup and meta-regression analyses revealed that heterogeneity might be related to disease type, ovarian stimulation protocol, and addition time of DHEA treatment. Moreover, DHEA administration was remarkably associated with improvements in endometrial makers (especially the EMT) and reproductive outcomes. Therefore, women with thin endometrium might benefit from the administration of DHEA. However, the evidence was insufficient to conclude that QoE was low to extremely low due to potential bias, imprecision and risk of heterogeneity between studies. Therefore, the findings of certain outcomes, particularly the number of transferred embryos, should be interpreted with caution.

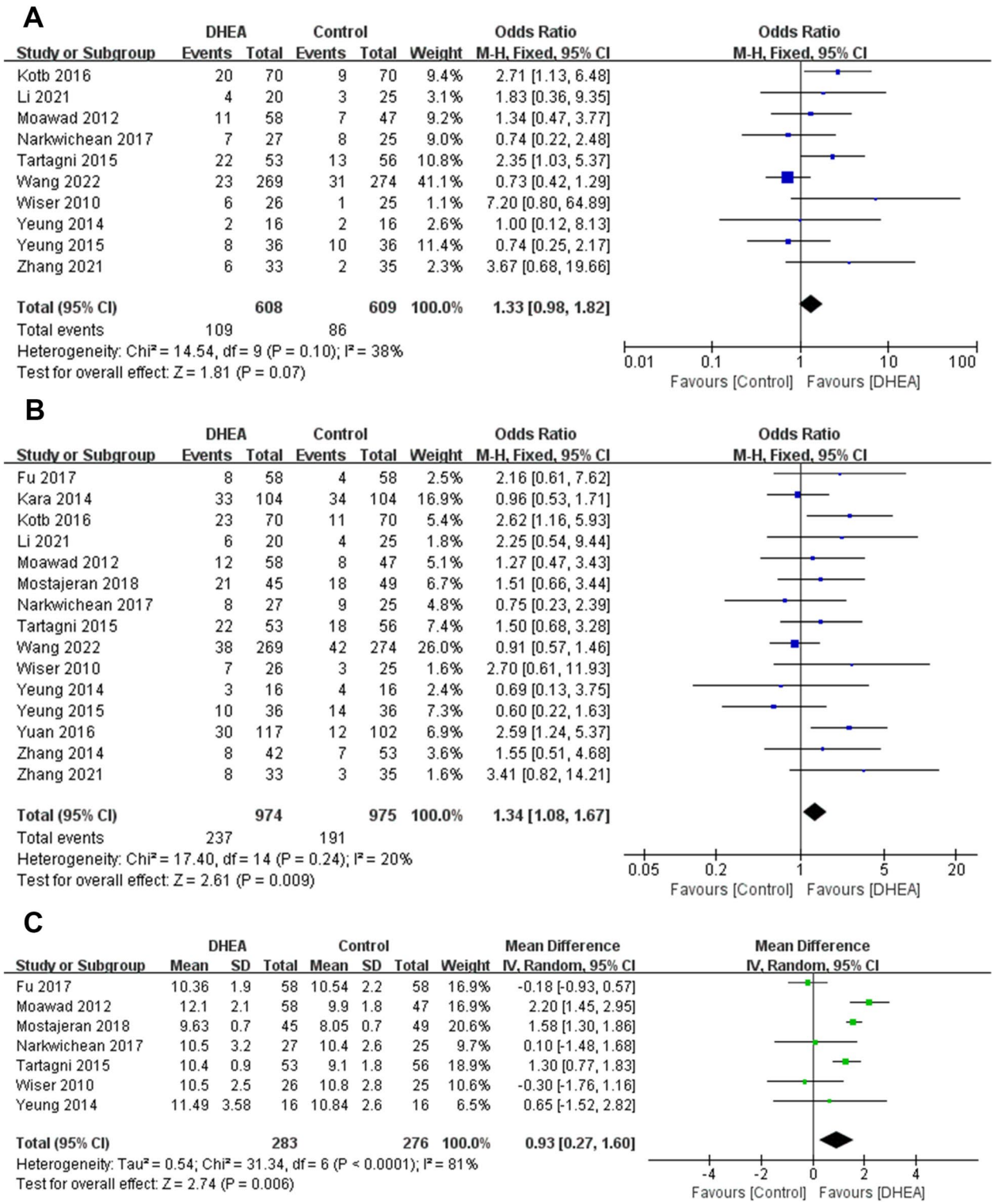

Fig. 2 (**A**) Forest plot for the meta-analysis of live birth rate/ongoing pregnancy rate; **B** Forest plot for the meta-analysis of clinical pregnancy rate; **C** Forest plot for the meta-analysis of endometrial thickness. CI, confidence interval; SD, standard differenc

Table 4 Effect estimate and heterogeneity of subgroup analysis for CPR

Subgroup	Trials (*n*)	Sample size (*n*)	Effect Estimate OR/MD (95% CI)	I^2	*P*
Average age					
≤40	13	1764	1.25 (0.99, 1.57)	13%	0.06
>40	2	185	2.53 (1.25, 5.13)	0%	0.01
Disease type					
POR	6	923	1.19 (0.85, 1.67)	29%	0.31
DOR	4	638	1.51 (1.02, 2.23)	37%	0.04
Normal	4	320	1.28 (0.81, 2.02)	3%	0.30
Endometriosis	1	68	3.41 (0.82, 14.21)	--	0.09
Ovarian stimulation protocol					
GnRH-a long protocol	5	374	1.57 (1.00, 2.46)	0%	0.05
GnRH-a short protocol	2	648	0.97 (0.63, 1.48)	0%	0.88
microflare stimulation	3	419	1.18 (0.74, 1.89)	0%	0.49
GnRH-A protocol	4	463	1.73 (1.11, 2.70)	61%	0.02
Addition time of DHEA treatment					
12w	9	991	1.40 (1.04, 1.88)	37%	0.03
8w	4	364	1.67 (1.02, 2.71)	0%	0.04
4–12w	1	543	0.91 (0.57, 1.46)	--	0.69
6–18w	1	51	2.70 (0.61, 11.93)	--	0.19

CI, confidence interval; DHEA, dehydroepiandrosterone; GnRH-A, gonadotrophin-releasing hormone antagonist; GnRH-a, gonadotrophinreleasing hormone agonist; CPR, clinical pregnancy rate; MD, mean difference; OR, odds ratio; POR, poor ovarian response; DOR, diminished ovarian reserve

Interpretation

EMT, endometrial pattern and perfusion play important roles in endometrial receptivity, as appropriate histological thickness is a necessary condition for embryo implantation, and suitable EMT is conducive to pregnancy [38]. Endometrial pattern is related to pregnancy and a reference index for clinical judgment of endometrial receptivity, and it has a certain clinical value [35]. Changes in uterine and ovarian arterial blood flow dynamics have predictive value for endometrial receptivity in women receiving ART [24]. Moreover, EMT has been shown to be positively correlated with CPR during the ART cycles. The endometrium thickens considerably during ovulation, and the implantation rate of fertilized embryos is high during this phase [4, 41]. Therefore, according to current clinical data, EMT might be a appropriate indicator to evaluate endometrial function.

DHEA is a commonly used androgen in clinical practice, and it plays an important regulatory role in various organ systems of the human body, such as protection of the nervous system, regulation of the immune system, prevention of osteoporosis, and inhibition of the development of atherosclerosis. It has been applied in ART for decades [17]. Recent evidence indicates that DHEA administration can improve endometrial function and pregnancy outcomes during IVF. DHEA promotes the development of early antral follicles and inhibits follicular atresia by increasing serum insulin-like growth factors-1 (IGF-1) levels [36]. It also increases the number of follicles in small antral and AMH levels [8]. Moreover, DHEA can improve mitochondrial function and reduce apoptosis of cumulus and granulosa cells [20]. Therefore, DHEA, as an estradiol precursor [8], can enhance the sensitivity of estrogen in the uterus, and may optimize the microenvironment of endometrial cells by regulating IGF-1. Moreover, DHEA treatment may improve endometrium receptivity by improving the antioxidant capacity of decidual endometrial stromal cells and endometrial HOXA-10 mRNA and androgen receptor expression [2, 33]. Additionally, we found that DHEA treatment showed more notable advantages in advanced-age women with DOR than in poor or normal responders. This indicates that advanced-age women with DOR, especially those with thin endometrium, would potentially benefit the most from DHEA administration.

Our findings suggest that DHEA markedly increases EMT and leads to better embryo implantation. According to the subgroup analyses, in advanced-age women with DOR, the effects of DHEA on the CPR were more pronounced when women were administered for 8 or 12weeks. Similarly, DHEA administered for 8 weeks was significantly associated with increased EMT. Moreover, the optimal duration of DHEA for improving oocyte and embryo quality was 8 or 12weeks. Therefore, DHEA-induced modification of endometrial function might play a critical rolein improving reproductive outcomes.

Table 5 Effect estimate and heterogeneity of subgroup analysis for EMT

Subgroup	Trials (*n*)	Sample size (*n*)	Effect Estimate OR/MD (95% CI)	I^2	*P*
Disease type					
POR	4	240	0.76 (−0.67, 2.20)	76%	0.30
DOR	1	116	−0.18 (−0.93, 0.57)	--	0.64
Normal	2	203	1.52 (1.27, 1.77)	0%	< 0.00001
Ovarian stimulation protocol					
GnRH-a long protocol	4	306	1.06 (0.41, 1.70)	68%	< 0.00001
GnRH-a short protocol	1	105	2.20 (1.45, 2.95)	--	0.88
microflare stimulation	1	116	−0.18 (−0.93, 0.57)	--	0.64
GnRH-A protocol	1	32	0.65 (−1.52, 2.82)	--	0.56
Addition time of DHEA treatment					
12w	3	189	1.15 (−0.35, 2.66)	70%	0.13
8w	3	319	0.96 (0.08, 1.84)	89%	0.03
6–18w	1	51	−0.30 (−1.76, 1.16)	--	0.69

CI confidence interval, *DHEA* dehydroepiandrosterone, *GnRH-A* gonadotrophin-releasing hormone antagonist, *GnRH-a* gonadotrophin-releasing hormone agonist, *EMT* endometrial thickness, *MD* mean difference, *OR* odds ratio, *POR* poor ovarian response, *DOR* diminished ovarian reserve

However, based on our own findings and the results of previous studies, the effect of DHEA administration on the LBR /ongoing pregnancy rate was unclear. Moreover, the results of sensitivity analysis showed that the EMT outcomes were unstable, which might be caused by the inconsistency of ultrasonic measurement time and method. Hence, recommending DHEA administration for women with thin endometrium might still be controversial.

To optimize IVF/ICSI results, several protocols have been proposed during the ovarian stimulation. GnRH agonist regiments have been widely used in IVF for decades. One of the most commonly used protocols is GnRH agonist long protocols, which are beneficial for increasing the CPR and number of retrieved oocytes, as well as for reducing cycle cancellation rates [46]. Consistent with previous studies, GnRH agonist long protocol combined with DHEA administration increased the EMT and the number of retrieved oocytes, fertilized oocytes, transferred embryos, and high-quality embryos compared to other ovarian stimulation protocols. GnRH agonists have a direct effect on the endometrium by regulating the expression of enzymes and cytokines to accelerate endometrial receptivity [3], consequently improving embryo implantation [6]. However, the application of GnRH-A protocol is also increasingly widely used, but there are few studies on GnRH-A protocol included in this analysis, hence, it would be important to focus on the effects of DHEA on patients treated with GnRH-A protocol in future studies.

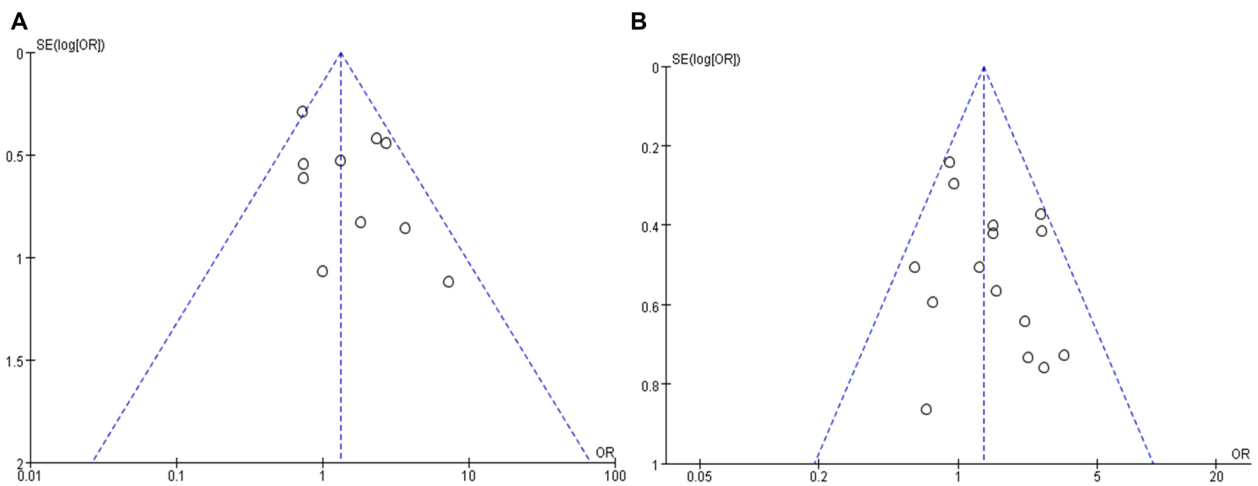

Fig. 3 Funnel plots of primary outcomes. **A** Live birth rate/ongoing pregnancy rate; **B** clinical pregnancy rate

Strengths and limitations

There are unique strengths in this research. To our knowledge, this is the first study to evaluate the effects of DHEA administration on endometrial and reproductive outcomes in women during IVF/ICSI. Previous studies mainly focused on DOR and pregnancy outcomes, and few studied the effects of DHEA in other populations and on endometrial function. For example, the comprehensive and systematic review with meta-analysis of Neves et al. [31] fouced on the impact of androgens (dehydroepiandrosterone/testosterone) on ovarian response and pregnancy outcomes in patients with diminished ovarian reserve and/or poor ovarian responders; the systematic review of Naik et al. [29] fouced on the pregnancy outcomes of DHEA and testosterone as pre- or co-treatments in infertile women undergoing assisted reproduction. Hence, to make this study more comprehensive, the study population and research perspective were expanded. Detailed subgroup analyses based on predefined factors were also performed to account potential sources of heterogeneity, identify appropriate population and optimal interventions to provide evidence for clinical practice. This study was registered with PROSPERO beforehand and conducted in strict accordance with the PRISMA statement. The program execution was reliable and the method quality was high.

However, there are some limitations to this study. First, clinical heterogeneity and potential for bias in various domains are inevitable due to differences in the definition of POR, study protocols, participant characteristics, and selection bias in original studies. And there are limited data for certain outcomes and unstable results in sensitivity analyses. Second, the quality of the original literature was low to very low, and many included studies were not originally designed or powered to measure the effect of DHEA on endometrial thickness, instead focusing primarily on ovarian response, this means: (1) observed effects on endometrial thickness may be incidental findings; (2) studies may not be adequately powered to detect meaningful differences in endometrial thickness; (3) lack of standardization in endometrial thickness measuring methods, timing, and reporting across studies; (4) timing of endometrial thickness measurements may not have been optimal for assessing the effect of DHEA; (5) other important markers of endometrial receptivity may have been overlooked. Hence, more studies including appropriate power calculations and standardized measurement protocols, with endometrial receptivity as the pre-specified outcome, are needed in the future to assess the effect of DHEA on endometrial function. For example, the EMT was considered the maximal anterior–posterior distance between both endometrial layers about 1 cm from the uterine fundus, subtracting the thickness of intrauterine fluid in the unlikely event that such was detected [34]. And the EMT was obtained on the day of human chorionic gonadotrophin administration, and was conducted by highly trained sonographers using vaginal transducer [14]. Third, the safety of DHEA supplementation could not be assessed because adverse events have been reported in only 10 studies. Therefore, further studies are needed to confirm the increased risk of adverse events when receiving exogenous DHEA. Forth, although we performed subgroup analyses, owing to the limited number of trials in some subgroups and small sample sizes, the data might not be sufficient to detect significant differences. Finally, to accurately and fundamentally evaluate the role of DHEA in IVF/ICSI, it is important to consider the LBR/ongoing pregnancy rate, as this is the ultimate indicator of efficacy in reproductive studies. However, in the present study, there was no statistical difference in the effect of DHEA on LBR/ongoing pregnancy rate due to the insufficient data, and the trial sequential analysis showed insufficient sample size for live birth rates.

Conclusion

Accumulatively, DHEA administration is not only associated with improved IVF/ICSI reproductive outcomes but is also beneficial for the endometrial function. The optimal duration of DHEA treatment is 8 or 12 weeks. Moreover, women with thin endometrium might benefit from DHEA intervention; therefore, if the standard treatment regimen does not achieve satisfactory results, adjuvant DHEA could be considered; and optimal DHEA intervention should be provided according to the individual needs and circumstances of patients. However, limited sample sizes, some methodological shortcomings, low quality of evidence, and high heterogeneity between studies significantly influenced the QoE and possible conclusions. Hence, the clinical recommendations of our data should be interpreted with caution, and the clinical application of DHEA in women with thin endometrium should also be cautious. More rigorous randomized controlled trials focused on live birth rates, endometrium, and safety outcomes with larger sample sizes are needed to further determine appropriate DHEA protocols (Supplementary Table S12).

Abbreviations

AMH	anti-Mullerian hormone
ART	assisted reproductive technology
CPR	clinical pregnancy rate
CIs	confidence intervals
DHEA	dehydroepiandrosterone
DOR	diminished ovarian reserve
EMT	endometrial thickness
FSH	follicle-stimulating hormone
GnRH-a	Gonadotropin-releasing hormone agonist
GnRH-A	gonadotropin-releasing hormone antagonist

GRADE	Grading of Recommendations Assessment, Development and Evaluation
IVF/ICSI	in vitro fertilization/intracytoplasmic sperm injection
LBR	live birth rate
MDs	mean differences
MR	miscarriage rate
ORs	Odds ratios
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	Prospective Register of Systematic Reviews
POR	poor ovarian response
QoE	quality of evidence
RCTs	randomized controlled trials

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13048-024-01581-3.

Supplementary Material 1. Supplementary Figure S1 Risk of bias of included studies. (A) Risk of bias graph; (B) Risk of bias summary.

Supplementary Material 2. Supplementary Figure S2 (A) Forest plot for the meta-analysis of miscarriage rate; (B) Forest plot for the meta-analysis of number of retrieved oocytes; (C) Forest plot for the meta-analysis of number of MII oocytes; (D) Forest plot for the meta-analysis of number of oocytes fertilized; (E) Forest plot for the meta-analysis of number of transferred embryos; (F) Forest plot for the meta-analysis of number of good quality embryos. CI, confidence interval; SD, standard difference.

Supplementary Material 3. Supplementary Figure S3 Trial sequential analysis for live birth rate/ongoing pregnancy rate (alpha = 0.05, beta = 0.20).

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

Supplementary Material 7.

Supplementary Material 8.

Supplementary Material 9.

Supplementary Material 10.

Supplementary Material 11.

Supplementary Material 12.

Supplementary Material 13.

Authors' contributions

MJ conceived the study and designed the study protocol. MJ and YG participated in the study selection. SL was involved in the data extraction and quality assessment. All authors contributed to the interpretation of the results. LH performed the statistical analysis and drafted the paper. All authors reviewed the manuscript and approved the final manuscript version to be published.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Author details

[1]School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China. [2]Department of Acupuncture, Wangjing Hospital of China Academy of Chinese Medical Sciences, Beijing 100101, China. [3]Department of Gastroenterology, Dongzhimen Hospital of Beijing University of Chinese Medicine, Beijing 100700, China. [4]Beijing Research Institute of Chinese Medicine, Beijing University of Chinese Medicine, No.11 Beisanhuandong Road, Chaoyang, Beijing 100029, P. R. China.

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